Please replace the paragraph at page 144, lines 1-6, to read as follows:

The software described in this manuscript is distributed as GENEHUNTER-PLUS™ (version 2.0 or later) and is available *via* anonymous ftp at galton.uchicago.edu on the /pub/kong directory. The allele-sharing method which is used is described in Kong and Cox (1997) and version 2.0 introduces an option to provide a family-specific weight in the lod score computation.

In the Claims

Please amend claims 18-21, 50-55 and 56-60 as follows:

18. (Amended) A method of screening for a modulator of calpain 10 function comprising:
    a) obtaining a calpain 10 polypeptide;
    b) determining a standard activity profile of the calpain 10 polypeptide;
    c) contacting the calpain 10 polypeptide with a putative modulator; and
    d) assaying for a change in the standard activity profile.

19. (Amended) The method of claim 18, wherein the calpain 10 polypeptide comprises amino acid 1 to 47 of SEQ ID NO:2.

20. (Amended) The method of claim 18, wherein obtaining the calpain 10 polypeptide comprises expressing the polypeptide in a host cell.

21. (Amended) The method of claim 20, wherein the calpain 10 polypeptide is isolated away from the host cell prior to contacting the calpain 10 polypeptide with the putative modulator.

50. (Amended) The method of claim 49, wherein the synthetic substrate is Suc-Leu-Tyr-amidomethylcoumarin (AMC).

51. (Amended) A method of screening for a modulator of calpain 10 function comprising:

a) obtaining an calpain 10 polypeptide;

b) contacting the calpain 10 polypeptide with a putative modulator; and

c) assaying for modulation of calpain 10 function by the putative modulator.

52. (Amended) The method of claim 51, wherein the calpain 10 polypeptide comprises the amino acid sequence of SEQ ID NO: 2.

53. (Amended) The method of claim 52, wherein the calpain 10 polypeptide has a sequence comprising amino acid 1 to 47 of SEQ ID NO:2,

54. (Amended) The method of claim 51, further comprising determining a standard activity profile of the calpain 10 polypeptide.

56. (Amended) The method of claim 55, wherein the synthetic substrate is Suc-Leu-Tyr-amidomethylcoumarin (AMC).

57. (Amended) The method of claim 55, wherein assaying for modulation of calpain 10 function comprises assaying for a change in the standard activity profile.

58. (Amended) The method of claim 51, wherein obtaining the calpain 10 polypeptide comprises expressing the polypeptide in a host cell.

59. (Amended) The method of claim 58, wherein the calpain 10 polypeptide is isolated away from the host cell prior to contacting the calpain polypeptide with the putative modulator.

60. (Amended) The method of claim 51, wherein obtaining the calpain 10 polypeptide comprises obtaining a cell containing the polypeptide.

Please add new claim 114 as follows:

--114. (New) The method of claim 18, wherein the calpain 10 polypeptide comprises the amino acid sequence of SEQ ID NO:2.--

II. RESPONSE TO OFFICE ACTION

A. Resubmission of Information Disclosure Statement and PTO 1449

As stated in the Action dated October 16, 2002, the Action contends that according to the PTO records, an IDS was filed on 3/26/2002, however no PTO form 1449 or copies of the references cited can be found in the application. Applicants have resubmitted herewith a copy of the PTO 1449 and the IDS mailed to the PTO on March 21, 2002 along with a copy of the transmittal letter and the postcard date stamped and returned by the PTO on March 26, 2001 provided herein as Exhibit F.

Applicants also bring to the attention of the Examiner that neither Applicants nor Applicants' representative were contacted prior to the Office Action dated October 16, 2002 to resubmit the PTO 1449 and the IDS missing from the application. It would therefore be improper for the PTO to issue a second and final action in the instant case, if such second action were in any way premised upon the art that was previously submitted. Furthermore, Applicants draw the attention of the Examiner to MPEP 706.07 which states:

> "Before final rejection is in order a clear issue should be developed between the examiner and applicant. To bring the prosecution to as speedy conclusion as possible and at the same time to deal justly by both the applicant and the public, the invention as disclosed and claimed should be thoroughly searched in the first action and the references fully applied; and in reply to this action the applicant should amend with a view to avoiding all the grounds of rejection and objection. Switching from one subject matter to another in the claims presented by applicant in successive amendments, or from one set of references to another by the examiner in rejecting in successive actions claims of substantially the same subject matter, will alike tend to defeat attaining the goal of reaching a clearly defined issue for an early termination, i.e., either an allowance of the application or a final rejection.
> While the rules no longer give to an applicant the right to "amend as often as the examiner presents new references or reasons for rejection," present practice does not sanction hasty and ill-considered final rejections. The applicant who is seeking to define his or her invention in claims that will give him or her the patent protection to which he or she is justly entitled should receive the cooperation of the examiner to that end, and not be prematurely cut off in the prosecution of his or her application."

B. Objections to the Drawings

The drawings have been objected to under 37 C.F.R. 1.84 or 1.152. Applicants have submitted herewith formal drawings 1/26 to 26/26. Please substitute drawings sheets 1/26 through 26/26 with drawings sheets 1/26 through 26/26 affixed hereto as Appendix E. Drawings sheets 1/26 through 26/26 are fully supported by the original drawings sheets 1/26 through 26/26. No new matter has been added.

C. Objections to the claims

Claims 50 and 56 are objected to because of the recitation of "Suc-Leu-Tyr-AMC." Applicants have amended claims 50 and 56 affixed hereto in Appendix C.

D. Status of the Claims

Due to a restriction Requirement dated January 10, 2002, Applicants elected without traverse to prosecute Group 1, claims 18-21 and 49-64 drawn to a method of screening for a modulator of calpain function in a Response to the Restriction Requirement filed April 8, 2002. Claims 18-21 and 49-64 were pending prior to the Office Action dated October 16, 2002. Claims 18-21 and 49-60 have been amended herein in Appendix C. Support for the amendments to the claims and specification may be found in the specification, claims, sequence listing and the figures as originally filed. No new matter has been added.

Therefore, the claims pending in the present application are claims 18-21 and 49-64, a copy of which is attached hereto for the Examiner's convenience in Appendix D.

E. Claim Rejection under 35 U.S.C. §112, second paragraph

1. Claims 18-21, 49-50, 54, and 57 are definite

Claims 18-21, 49-50, 54 and 57 are rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. The Action contends that claims 18-21 and 49-50 are rejected under 35 U.S.C. §112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. The Action further contends that no step is disclosed for correlating a change in the standard activity profile and the presence of a modulator.

The Applicants traverse this rejection. Applicants state that no step has been omitted in claims 18-21 and 49-50. The Applicants further state that claim 18, as amended, recites "A method of screening for a modulator of calpain 10 function comprising: a) obtaining a calpain 10 polypeptide; b) determining a standard activity profile of the calpain 10 polypeptide; c) contacting the calpain 10 polypeptide with a putative modulator; and d) assaying for a change in the standard activity profile," and need not be further amended to recite the additional step of "assaying for a change in the standard activity profile is an indication of the presence of the modulator," as stated by the Action. The Applicants further argue that it would be know by one of ordinary skill in the art, that the steps the Action cites as being omitted are already implied by the claims as originally filed in the instant application. For instance, step (b) as recited in claim 18 which determines the standard activity profile of the calpain 10 polypeptide, provides the basal activity. One of skill in the art would know that this provides a measure from which to quantitate the change in activity. Step (c) of claim 18 recites "contacting the calpain 10 polypeptide with a putative modulator," and step (d) of claim 18 recites "assaying for a change in

the standard activity profile." One of ordinary skill in the art would know, given steps (c) and (d) of claim 18 that a calpain 10 polypeptide is contacted with a modulator then a change in the standard activity is assayed for. It would be further understood to one of skill in the art that the difference in the standard activity assayed in step (b) and step (d) would be indicative of the presence of the modulator of step (c). Thus, the Action is erroneous in stating that an essential step is omitted and is also presumptive in reading its own suggestive language into the claims since the Applicants have clearly stated the necessary steps in the claims as originally written. Moreover, because the alleged missing step is not in fact an actual step to be performed, it does not limit the claim in any meaningful way. The claim's actual recited steps remain the same. Therefore, the rejection is inappropriate and should be withdrawn.

2. Claims 18, 54, and 57 are definite

The Action further contends that claims 18, 54 and 57 are indefinite in the recitation of "standard activity profile" as it is unclear, absent a statement defining the term. Applicants traverse this rejection.

Applicants argue that claims 18, 54 and 57 are definite and state that a claim is only indefinite if one of skill in the art would not understand what is claimed in light of the specification. The specification at page 7, lines 17-19, states: "The standard activity profile of the calpain 10 polypeptide may be determined by measuring the binding of the calpain 10 polypeptide to a synthetic substrate. An example of such a synthetic substrate is Suc-Leu-Tyr-AMC (Vilei *et al.*, 1997)." Furthermore, as stated above, no step(s) is omitted from claim 18, but rather that the step(s) is written into the claim as originally filed. The Applicants also state that claim 49 which recites "The method of claim 19, wherein the standard activity profile of the

calpain 10 polypeptide is determined by measuring the binding of the calpain 10 polypeptide to a synthetic substrate" further limits claim 18. Claim 55 which recites "The method of claim 54, wherein the standard activity profile of the calpain 10 polypeptide is determined by measuring the binding of the calpain 10 polypeptide to a synthetic substrate" further limits claim 54; and claim 57 which recites "The method of claim 55, wherein assaying for modulation of calpain function comprises assaying for a change in the standard activity profile" further limits claim 54. Thus, the claims as written clearly define the term "standard activity profile." The specification also defines "standard activity profile". Therefore, the rejection of claims 18, 54 and 57 as indefinite is made moot.

In light of the foregoing, the Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 18-21, 49-50, 54 and 57 under 35 U.S.C. §112, second paragraph.

F. Claim Rejections under 35 U.S.C. §112, first paragraph

1. Rejection of Claims 18-21, 49-52, and 54-64 is overcome

Claims 18-21, 49-52, and 54-64 are rejected as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Action also contends that no disclosure of the structure of other calpain polypeptides as encompassed by the claims has been provided which would allow one of skill in the art to practice the scope of the claimed method. The Action further contends that no disclosure of the critical structural elements a polypeptide should have to display calpain activity has been provided.

Applicants traverse the rejection and cite the amended claims provided in Appendix C along with the following evidence that the Applicants were in possession of the claimed invention at the time of the filing of the present application.

To satisfy the written description requirement, possession of the invention is shown by describing all its claimed limitations, not that which is obvious (*Vas-Cath Inc. v. Mahurkar,* 19U.S.P.Q.2d 1111,1117 (Fed.Cir.1991). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.,* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including . . . by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. *See, e.g., Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991); MPEP 2163.

Claim 18 and claim 51, from which claims 19-21, 49-50, and 52-60 depend, recite a "calpain 10 polypeptide." At page 29, lines 18-30, and pages 30-31. Applicants have provided more than adequate description of the calpain 10. At these pages, Applicants disclose the full length of calpain 10 and its various exon regions that are differentially spliced to create different calpain 10 isomers. Applicants also provide Table 1, at page 30 which describes the calpain 10 isoforms with indication as to the encoded exons, the polypeptide length and the sequences corresponding to the SEQ ID Nos. In FIG. 1, Applicants have diagrammed the alternative spliced forms of calpain 10 indicating the various domains. In FIG. 5, Applicants have also

provided an alignment of calpain 10 and various calpains indicating the domains. On page 31, Applicants provide a structural description of the domains of calpain 10, such as the specific calmodulin-like Ca^{2+} binding domain. In FIG. 6, Applicants have provided a phylogentic tree of the calpain large subunit. At pages 26, 148, 149, and Example 8, Applicants have provided support, as is known in the art, that calpains are a family of structurally related intracellular multidomain cysteine proteinases containing a papain-related catalytic domain, whose activity depends on calcium. Applicants have also provided in the sequence listing the amino acid sequences of calpian 10 and its isoforms. Given the more than adequate description provided in the specification and figures, it would be clear to one of skill in the art that the Applicants had possession of the claimed invention at the time of filing sufficient to practice the invention.

2. Claims 18-21, 49-52, and 54-64 are enabled

The Action further contends that claims 18-21, 49-52 and 54-64 are rejected under 35 U.S.C. §112, first paragraph because the specification, while being enabling for a method of screening for inhibitors of the human calpain polypeptide of SEQ ID NO: 2, does not reasonably provide enablement for a method of screening for inhibitors of any calpain. The Action further contends that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants traverse the rejection and cite the amended claims provided in Appendix C along with the following arguments for the lack of enablement, as in the written description above. Applicants have provided ample teaching with respect to a calpain 10 polypeptide on page 29, lines 18-30 and pages 30-31. At these pages, Applicants disclose the full length of

calpain 10 and its various exon regions that are differentially spliced to create different calpain 10 isomers. Table 1, on page 30 of the specification also describes the calpain 10 isoforms indicating the encoded exons, the polypeptide length, and the sequences corresponding to the SEQ ID NOs. In FIG. 1, Applicants have diagrammed the alternative spliced forms of calpain 10 indicating the various domains. In FIG. 5, Applicants have also provided an alignment of calpain 10 and various calpains indicating the domains. On page 31, Applicants provide a structural description of the domains of calpain 10, such as the specific calmodulin-like Ca^{2+} binding domain. Applicants have provided working examples in the specification on pages 123 to pages 165 which clearly describes how to make and use the invention. Applicants have provided the sequences of calpain 10 polypeptide and its isoforms in the Sequence Listing of the application as originally filed. Applicants have provided relevant teachings to identify characteristics and functionality of calpain 10 and its isoforms, as well as the cloning and the localization of calpain 10 in the Examples of the Specification. In addition, in the Examples on pages 123-165, Applicants have provided the use of calpain 10 in detecting and analyzing polymorphisms in individuals.

The Applicants contend that the enablement requirement is met by describing any mode of enablement of the invention. Thus, the Applicants have provided evidence that makes moot the rejection of the claims as lacking enablement from the specification, figures and the sequence listing as described above. Furthermore, Applicants' amendments to the claims as provided in Appendix C herein, renders the rejection under 35 U.S.C. §112 first paragraph, as lacking enablement, moot.

In light of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 18-21, 49-52 and 54-64 under 35 U.S.C. §112 first paragraph.

G. Claims 18, 20-21, 51, and 58-60 are rejected under U.S.C. 102(b) as being anticipated by Meyer *et. al.*

The Action contends that Meyer *et al.* teaches the cloning, expression and characterization of human calpain I using the baculovirus expression system. The Action also contends that Meyer *et al.*, teaches the characterization of the recombinant calpain I by testing different inhibitors of calpain activity. The Action also contends that the method for screening inhibitors (modulators) of clapain I taught by Meyer *et. al.* requires (1) combining the recombinant calpain with a substrate (succinyl(Suc)-Leu-Tyr-methoxynaphthylamine MNA, (2) measuring the activity of the recombinant calpain against the substrate in the absence of the inhibitor, (3) measuring the activity of the recombinant calpain against the substrate in the presence of the inhibitor and (4) determining the change activity by comparison of the activity in the absence and presence of the inhibitor. The Action contends the recombinant calpain is recombinantly expressed in insect cells. The Action further contends that claims 18, 20-21, 51, 54 and 58 are drawn to a method of screening for modulators of calpain activity wherein a calpain polypeptide obtained by any method or recombinantly, is contacted with the substrate in the absence and presence of a modulator, the activity is measured in the presence and absence of the modulator and a change in activity is correlated with the presence of the modulator. The Action further contends that claims 59-60 are drawn to the method described above wherein the calpain polypeptide is obtained by isolating a cell containing said polypeptide. The Action contends that since the recombinant calpain of Meyer *et al.* is expressed in insect cells the

recombinant calpain is contained by a cell, therefore the teachings of Meyer *et al.* anticipates the claims as written. Applicants traverse this rejection.

For a prior art reference to anticipate, every element of the claimed invention must be identically shown in a single reference. These elements must be arranged as in the claim under review, but this is not an "ipsissimis verbis" test. *In re Bond,* 910 F.2d 831,15 U.S.P.Q.2d 1566,1567,1568 (Fed.Cir.1990).

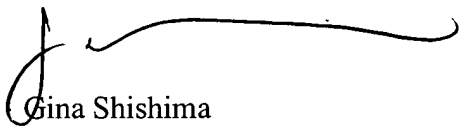
Applicants argue that Meyer *et al.* does not teach a method of screening for a candidate modulator of calpain 10 as is claimed by the present invention. Rather, Meyer *et al.* teach a method for the production of a recombinant human calpain 1 as a means of studying and elucidating the mechanism of native human calpain 1. Furthermore, Meyer *et al.* does not teach the calpain 10 polypeptide of the claimed invention, much less one comprising amino acids 1 to 47 of SEQ ID NO: 2. Applicants further argue that it would not be obvious to one of skill in the art given Meyer *et al.* to obtain or use the polypeptides of Applicants invention since Meyer *et al.* does not disclose how to obtain calpain 10 polypeptides but rather the production of a recombinant calpain 1. Thus, Applicants argue that Meyer *et al.* does not anticipate the present invention.

H. Conclusion

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants respectfully request that the rejection of all claims be withdrawn so the may pass to issuance.

The Examiner is invited to contact the undersigned attorney at 512-536-3081 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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